Elevated Depressive Symptoms, Antidepressant Use, and Diabetes in a Large Multiethnic National Sample of Postmenopausal Women

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OBJECTIVE—To examine elevated depressive symptoms and antidepressant use in relation to diabetes incidence in the Women's Health Initiative.

RESEARCH DESIGN AND METHODS—A total of 161,808 postmenopausal women were followed for over an average of 7.6 years. Hazard ratios (HRs) estimating the effects of elevated depressive symptoms and antidepressant use on newly diagnosed incident diabetes were obtained using Cox proportional hazards models adjusted for known diabetes risk factors.

RESULTS—Multivariable-adjusted HRs indicated an increased risk of incident diabetes with elevated baseline depressive symptoms (HR 1.13 [95% CI 1.07–1.20]) and antidepressant use (1.18 [1.10–1.28]). These associations persisted through year 3 data, in which respective adjusted HRs were 1.23 (1.09–1.39) and 1.31 (1.14–1.50).

CONCLUSIONS—Postmenopausal women with elevated depressive symptoms who also use antidepressants have a greater risk of developing incident diabetes. In addition, longstanding elevated depressive symptoms and recent antidepressant medication use increase the risk of incident diabetes.

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Adults with depression have an increased risk of developing diabetes (1,2). Antidepressant medication use has been implicated in the relationship between depression and diabetes (3–6), although few studies have investigated the independent effect of depression and antidepressant use (4,6). Using Women's Health Initiative (WHI) data, we tested the hypotheses that *1*) elevated depressive symptoms and antidepressant use would each be independently associated with an increased risk of diabetes, and *2*) the combination of elevated depressive symptoms and antidepressant use would have a compounded effect on incident diabetes risk.

RESEARCH DESIGN AND METHODS

—The WHI enrolled 161,808 participants into clinical trials and an observational study (WHI-OS group) (7–10). Medication use, depressive symptoms, and diabetes status were collected repeatedly over an average of 7.6 years of follow-up. The study was approved by the institutional review boards of participating WHI institutions, and institutional review board exemption for the current investigation was obtained at the University of Massachusetts Medical School.

Diabetes status was determined by self-report of ever having received a physician diagnosis of and/or treatment for diabetes when not pregnant. Diabetes status was recorded at baseline and annually. This method is a reliable indicator of diagnosed diabetes, validated with medication and laboratory data assessments (11). Time to diabetes was calculated as the interval between the enrollment date and the earliest of the following: *1*) the date of the annual medical history update when new diabetes status was ascertained (positive outcome); 2) the date of the last annual medical update during which diabetes status could be ascertained (censorship); or 3) the date of death (censorship).

Depressive symptoms at baseline and year 3 were measured using the Center for Epidemiological Studies Depression Scale (CES-D) six-item form (12). A cut point of five or higher categorized subjects as having elevated depressive symptoms (13). Medication names from container labels provided by participants were matched to the Master Drug Database (Medi-Span, Indianapolis, IN) at baseline and year 3. Based on the Master Drug Database classification, a binary indicator for antidepressant medication use was created.

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Statistical analyses

Among 152,250 women who were reported to not have diabetes at baseline and who had complete relevant data at baseline, Cox proportional hazards models were used to model the instantaneous hazard of diabetes as a function of elevated depressive symptoms and antidepressant medication use. Models were stratified on the WHI participant condition to allow for varying baseline hazard functions in relation to elevated depressive symptoms and antidepressant use within the WHI-OS and the different WHI clinical trial arms. The multivariate model adjusted for potential confounders including age, race/ethnicity, education, smoking status, BMI, recreational physical activity, alcohol intake, dietary energy intake, family history of diabetes, and hormone therapy use.

Longitudinal analysis was based on a subset of 70,874 women from the WHI-OS arm with data available on both depressive symptoms and antidepressant use. Elevated depressive symptoms at baseline and the year 3 visit were coded as follows: 0 = never any depressive symptoms (reference category); 1 = depressive symptoms at baseline only; 2 = depressive symptoms at year 3 only; and 3 = depressive symptoms at baseline and year 3. Antidepressant use was coded similarly. Evidence of a multiplicative interaction effect at baseline and longitudinally was assessed in Cox proportional hazards models that included main effects and a multiple interaction term.

RESULTS—At baseline, 15.5% of women were above the depression cutoff on the CES-D and were defined as having elevated depressive symptoms, and 6.9% of women reported using antidepressants. The cumulative incidence of self-reported diabetes was 6.7%. Self-reported diabetes incidence rates were 8.6% for women with elevated depressive symptoms and 6.3% for those without (Table 1). In unadjusted models, elevated depressive symptoms were significantly related to diabetes risk (hazard ratio [HR] 1.38 [95% CI 1.32–1.45]). The multivariate-adjusted HR was 1.13 (1.07–1.20). Antidepressant use also was significantly related to diabetes risk (unadjusted HR 1.30 [1.22–1.40]; multivariate-adjusted HR 1.18 [1.10–1.28]). Self-reported diabetes incidence rates by combinations of elevated depressive symptoms and antidepressant use at baseline were 6.3% for those not taking antidepressants and below the CES-D cutoff, 7.6% for those taking antidepressants and below the CES-D cutoff, 8.4% for those above the CES-D cutoff and not taking antidepressants, and 9.6% for those above the CES-D cutoff and taking antidepressants ($P < 0.001$). There was no evidence of a significant multiplicative interaction between elevated depressive symptoms and antidepressant use.

Compared with those who were never depressed and never used antidepressants, the risk of diabetes was higher for those who reported elevated depressive symptoms and used antidepressants at baseline and year 3 (Table 1). After adjustment for multiple covariates, only HRs for those who reported elevated depressive symptoms at baseline and year 3 remained significant (multivariate-adjusted HR 1.23 [95% CI 1.09–1.39]), whereas HRs for those who reported antidepressant use only at year 3 (1.44 [1.26–1.66]) and who reported antidepressant use at both time points were significant (1.31 [1.14–1.50]). There was no evidence of a significant multiplicative interaction between longitudinal measures of elevated depressive symptoms and antidepressant use. Although the test of the proportional hazards assumption failed ($P < 0.001$), elevated depressive symptoms and antidepressant use were found to be significantly associated with diabetes risk in accelerated failure time models that allowed nonproportional hazards over time.

Table 1—*HRs of diabetes associated with elevated depressive symptoms and antidepressant medication use at baseline and the year 3 visit in the WHI, estimated from Cox proportional hazards models*

Primary exposure variable	(*n* [self-reported incident diabetes %])	Unadjusted HR (95% CI)*	HR (95% CI) adjusted for age and race†	HR (95% CI) from the multivariate model‡
Baseline analyses (*n* = 152,250)				
Elevated depressive symptoms				
Yes	(23,541 [8.6])	1.38 (1.32–1.45)	1.34 (1.27–1.41)	1.13 (1.07–1.20)
No	(128,709 [6.3])	1.00	1.00	1.00
Antidepressant medication use				
Yes	(10,512 [8.2])	1.30 (1.22–1.40)	1.42 (1.32–1.52)	1.18 (1.10–1.28)
No	(141,738 [6.6])	1.00	1.00	1.00
Longitudinal analyses (*n* = 70,874)				
Elevated depressive symptoms				
At baseline and year 3	(4,554 [8.32])	1.74 (1.57–1.94)	1.67 (1.50–1.86)	1.23 (1.09–1.39)
At baseline only	(5,691 [5.96])	1.22 (1.09–1.36)	1.21 (1.08–1.35)	0.99 (0.87–1.12)
At year 3 only	(6,625 [6.37])	1.32 (1.19–1.46)	1.31 (1.18–1.45)	1.06 (0.95–1.18)
Never	(54,004 [4.92])	1.00	1.00	1.00
Antidepressant medication use				
At baseline and year 3	(3,466 [7.24])	1.46 (1.28–1.66)	1.60 (1.41–1.82)	1.31 (1.14–1.50)
At baseline only	(1,530 [5.75])	1.14 (0.92–1.41)	1.19 (0.96–1.47)	0.92 (0.73–1.15)
At year 3 only	(3,223 [7.51])	1.50 (1.32–1.71)	1.61 (1.42–1.84)	1.44 (1.26–1.66)
Never	(62,655 [5.13])	1.00	1.00	1.00

*Cox proportional hazards model including elevated depressive symptoms or antidepressant use. †Cox proportional hazards model including elevated depressive symptoms or antidepressant use, while adjusting for age and race/ethnicity. ‡Cox proportional hazards model, including both elevated depressive symptoms and antidepressant use jointly, while adjusting for age, race/ethnicity, education, smoking status at baseline, BMI, hours of recreational activity per week, alcohol intake, total daily energy intake, family history of diabetes, and hormone therapy use.

CONCLUSIONS—Elevated depressive symptoms and antidepressant use at baseline were independently associated with an increased risk of diabetes among postmenopausal women, but there was no compounded effect of elevated depressive symptoms and antidepressant use. Our longitudinal analyses indicate that only longstanding elevated depressive symptoms increase the risk of incident diabetes, whereas antidepressant use at 3 years is associated with a dramatically elevated risk regardless of its presence at baseline. Recent antidepressant medication may increase risk of incident diabetes.

Because self-report of diabetes incidence may be imprecise, we conducted sensitivity analyses using a fasting glucose ≥126 mg/dL to identify diabetes. Although results were not significant likely because of small sample size, the trends observed were similar to analysis results using self-reported diabetes. Because elevated depressive symptoms were assessed at only two time points, some cases may have been missed (14). Likewise, women who began and then discontinued antidepressants in between collection points would be missed. However, antidepressants often are used long-term (for ~5–7.5 years) (15).

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No potential conflicts of interest relevant to this article were reported.

Y.M. wrote the manuscript and researched data. R.B. performed data analyses and reviewed and edited the manuscript. S.L.P., K.L.S., A.L.C., B.O., L.T., S.L., M.S., D.M.S., M.C.R., J.K.O., M.C., and J.R.H. contributed to discussion and reviewed and edited the manuscript. M.Z. performed data analyses and reviewed and edited the manuscript.

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